EXHIBIT 22

MAYO CLINIC

ORIGINAL ARTICLE

Stroke Risk and Outcomes in Patients With Traumatic Brain Injury: 2 Nationwide Studies

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Abstract

Objective: To investigate whether patients with traumatic brain injury (TBI) have an increased risk of stroke or poststroke mortality.

Participants and Methods: Using Taiwan's National Health Insurance Research Database, we conducted a retrospective cohort study of 30,165 patients with new TBI and 120,660 persons without TBI between January 1, 2000, and December 31, 2004. The risk of stroke was compared between 2 cohorts through December 31, 2008. To investigate the association between in-hospital mortality after stroke and history of TBI, we conducted a case-control study of 7751 patients with newly diagnosed stroke between January 1, 2005, and December 31, 2008.

Results: The TBI cohort had an increased stroke risk (hazard ratio [HR], 1.98; 95% CI, 1.86-2.11). Among patients with stroke, those with a history of TBI had a higher risk of poststroke mortality compared with those without TBI (odds ratio, 1.57; 95% CI, 1.13-2.19). In the TBI cohort, factors associated with stroke were history of TBI hospitalization (HR, 3.14; 95% CI, 2.77-3.56), emergency care for TBI (HR, 3.37; 95% CI, 2.88-3.95), brain hemorrhage (HR, 2.69; 95% CI, 2.43-2.99), skull fracture (HR, 3.00; 95% CI, 2.42-3.71), low income (HR, 2.65; 95% CI, 2.16-3.25), and high medical expenditure for TBI care (HR, 2.26; 95% CI, 2.09-2.43). The severity of TBI was also correlated with poststroke mortality.

Conclusions: Traumatic brain injury was associated with risk of stroke and poststroke mortality. The relationship between TBI and poststroke mortality does not seem to transcend all age groups. This research shows the importance of prevention, early recognition, and treatment of stroke in this vulnerable population.

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Stroke is the second leading cause of death worldwide and the leading cause of acquired disability in adults in most regions.[1-3] Cardiac disease, hypertension, diabetes, smoking, alcohol intake, unhealthy diet, abdominal obesity, lack of exercise, psychosocial stress, and depression are risk factors associated with 90% of stroke risk.[3] Previous studies identified several risk or protective factors for stroke and poststroke complications.[4-8] Nevertheless, other potential risk factors associated with stroke prevalence need further validation.

Traumatic brain injury (TBI) is a common trauma in the United States; it affects an estimated 1.7 million patients annually (1.365 million emergency care visits, 275,000 hospitalizations, and 52,000 deaths).[9] The socioeconomic effects of disability after TBI are potentially long term or lifelong.[10-18] A lot is known about the epidemiologic features, natural history, and risk factors of TBI.[9,19-22] However, the high TBI fatality rate and post-TBI complications are still serious concerns.[23]

The health effects after TBI include neurologic disorders, cognitive impairment, psychiatric illness, poor social functioning, and other adverse outcomes (such as brain tumor and mortality).[15-18] A previous study investigated the increased risk of stroke in individuals who survived TBI.[24] However, whether severity of TBI is associated with stroke is still unknown. Another recent study was limited by focusing on ischemic stroke.[25] No information was available on the association between TBI and poststroke mortality in patients with stroke. We evaluated the association between TBI and a new-onset stroke event in a case-control study and conducted a nested case-control study to identify whether TBI contributes to poststroke mortality.

PARTICIPANTS AND METHODS

Source of Data

The Department of Health of Taiwan in 1995 integrated 13 insurance systems into a universal coverage health care program that covered

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more than 99% of the nation's 23 million people by the end of 2008. The claims data included patients' personal characteristics and records for all medical services, outpatient and inpatient, from 1996 to 2008. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) was used for diagnosing the diseases. Taiwan's National Health Research Institutes provides the National Health Insurance Research Database for public access. Patient information, including date of birth, sex, residence, and income (inferred from insurance fees), was retrieved, and the validity of the database has been verified.[26] The National Health Insurance Bureau conducts regular sample cross-checks of each hospital's claims with medical records and administers punitive measures for coding infractions, followed by tying a hospital's reimbursement level to its patient severity profile. Thus, hospitals' interests are best served by accurate coding of diagnoses and care items, and the precision of major diagnosis codes, procedure codes, and underlying cause of death in the National Health Insurance Research Database is generally recognized.

Ethical Approval

Insurance reimbursement claims used in this study were from Taiwan's National Health Insurance Research Database, which is available for public access. This study was conducted in accordance with the Helsinki Declaration. To protect personal privacy, the electronic database was decoded, with patient identifications scrambled for further public access for research. According to National Health Research Institutes regulations, informed consent is not required because of the use of decoded and scrambled patient identification. However, this study was evaluated and approved by Taiwan's National Health Research Institutes.[27-29]

Study Design and Population

In the random sample of 1 million insured people, we conducted a retrospective cohort study of 30,165 patients with newly diagnosed TBI (*ICD-9-CM* codes 800, 801, 803, 804, and 850-854) and 120,660 persons without TBI aged 20 years and older between January 1, 2000, and December 31, 2004, with exclusion of relevant diagnoses of TBI and stroke (*ICD-9-CM* codes 430-437) before the index date. The TBI and non-TBI cohorts were frequency matched by age and sex and were followed up from the index date until December 31, 2008, or until being censored. Follow-up, in person-years, was calculated for each participant until the diagnosis of stroke or until being censored because of death, withdrawal from the insurance system, or loss to follow-up. The non-TBI group included the remaining people who did not have a history of TBI throughout follow-up. In addition, to focus on long-term risk of stroke after TBI, patients who died within 30 days after TBI were also excluded.

In the same data set, we conducted a case-control study and used the diagnosis codes of the *ICD-9-CM* to identify 7751 patients with new-onset stroke (*ICD-9-CM* codes 430-437) between January 1, 2005, and December 31, 2008. Patients with stroke and in-hospital mortality were considered the case group, and stroke survivors were considered the control group. Stroke cases and controls had no history of diagnosis of stroke by a physician before the index date. We identified the history of TBI (*ICD-9-CM* codes 800, 801, 803, 804, and 850-854) during the 24 months before stroke for stroke fatal cases and survival controls.

Measures and Criteria

Based on previous studies,[4-8,27-29] sociodemographic factors (such as age, sex, urbanization, and low-income status) and coexisting medical conditions (such as hypertension [*ICD-9-CM* codes 401-405], diabetes [*ICD-9-CM* code 250], mental disorders [*ICD-9-CM* codes 290-319], chronic obstructive pulmonary disease [COPD] [*ICD-9-CM* codes 490-496], hyperlipidemia [*ICD-9-CM* codes 272.0, 272.1, and 272.2], parkinsonism [*ICD-9-CM* code 332], migraine [*ICD-9-CM* code 346], epilepsy [*ICD-9-CM* code 345], alcohol-related illness, renal dialysis, and smoking cessation) were analyzed for their potential association with TBI and stroke.

We defined alcohol-related illnesses, including alcoholic psychoses (*ICD-9-CM* code 291), alcohol dependence syndrome (*ICD-9-CM* code 303), alcohol abuse (*ICD-9-CM* code 305), alcoholic fatty liver (*ICD-9-CM* code 571.0), acute alcoholic hepatitis (*ICD-9-CM* code 571.1), alcoholic cirrhosis of the liver (*ICD-9-CM* code 571.2), and alcoholic liver damage (*ICD-9-CM* code 571.3).[4] The age of

the study case was defined when the stroke event occurred; the age of the control was coincident with the timing of stroke cases selected. The population density was defined by dividing the 359 Taiwan townships and city districts' populations by the area of each administrative unit and categorizing them into four quartiles as areas of low, moderate, high, and very high urbanization.[4-8,27-29] Low income was defined as qualifying for waived medical copayments as certified by the Bureau of National Health Insurance.[4,7,8,27-29]

According to previous reports,[14,28,29] we assessed whether different types of TBI (including skull fracture [*ICD-9-CM* codes 800, 801, 803, and 804], mild TBI [*ICD-9-CM* code 850], or severe TBI [*ICD-9-CM* codes 851-854]), brain hemorrhage (*ICD-9-CM* codes 852.2, 852.3, 852.4, 852.5, 852.0, 852.1, and 853), or loss of consciousness were associated with stroke and poststroke mortality. We also examined the frequency of prestroke emergency services (1 or ≥2 times) and hospitalization (length of stay <7 or ≥7 days) for TBI during the 24 months before stroke as potential indicators of disease severity associated with poststroke mortality. To evaluate prestroke TBI-related medical expenditure as a potential indicator of disease severity associated with stroke, medical expenditures for prestroke TBI care during the 24 months before stroke were categorized into low (the lowest quartile), moderate (the third quartile), and high (the first and second quartiles) medical expenditure. This study further examined the effects of post-TBI migraine in association with TBI and stroke. The impact of low-income status on the risk of stroke and poststroke mortality was examined in patients with TBI. We also considered brain hemorrhage or loss of consciousness as the severity of TBI in association with stroke and poststroke mortality.

Statistical Analyses

We compared sociodemographic factors (such as age, sex, urbanization, and low income), coexisting medical conditions (such as hypertension, diabetes, mental disorders, COPD, hyperlipidemia, parkinsonism, migraine, epilepsy, renal dialysis, smoking cessation, and alcohol-related illnesses), and new-onset stroke between the TBI and non-TBI cohorts using the χ^2 test. The sociodemographic features and coexisting medical conditions were also compared between patients with stroke who died and survivors by the χ^2 test. We used the Cox proportional hazards model to calculate adjusted hazard ratios (HRs) and 95% CIs for stroke between the TBI and non-TBI cohorts during follow-up. Multivariate logistic regression analysis was used to estimate odds ratios (ORs) and 95% CIs for poststroke mortality associated with TBI during the 24 months before stroke after controlling for age, sex, urbanization, low income, hypertension, diabetes, mental disorders, COPD, hyperlipidemia, parkinsonism, migraine, epilepsy, renal dialysis, smoking cessation, and alcohol-related illnesses. Based on a recent study,[25] we calculated the HR for stroke in patients with TBI by excluding stroke after TBI within 7 and 30 days.

We calculated adjusted ORs and 95% CIs for poststroke mortality in association with types of TBI, brain hemorrhage, and loss of consciousness. By using multivariate logistic regression analyses and adjusting for age, sex, urbanization, low income, hypertension, diabetes, mental disorders, COPD, hyperlipidemia, parkinsonism, migraine, epilepsy, renal dialysis, smoking cessation, and alcohol-related illnesses, we also calculated the stroke risk and poststroke mortality associated with patients with TBI during the 24 months before stroke who had low-income status, migraine, prestroke medical expenditures for TBI care, and a history of emergency care or hospitalization for TBI. All the analyses were performed using SAS for Windows (version 9.1; SAS Institute, Inc), and 2-sided $P<.05$ was taken to represent statistical significance.

RESULTS

In the retrospective cohort study, the proportion of new-onset stroke was higher in the TBI cohort than in the non-TBI cohort (4.8% vs 2.4%, $P<.001$) (Table 1). Compared with the non-TBI group, patients with TBI were more likely to live in less-urbanized areas (30.7% vs 26.1%) and to have a low-income status (4.1% vs 1.9%), mental disorders (38.7% vs 23.6%), hypertension (24.5% vs 22.0%), COPD (20.1% vs 15.0%), hyperlipidemia (12.7% vs 11.5%), diabetes (11.9% vs 9.0%), migraine (11.8% vs 6.6%), alcohol-related disease (3.8% vs 1.1%), parkinsonism (3.1% vs 1.4%), epilepsy (2.8% vs 0.6%),

TABLE 1. Sociodemographic Factors, Coexisting Medical Conditions, and Stroke in Cohorts With and Without TBI[a,b]

Characteristic	Non-TBI cohort (n=120,660)	TBI cohort (n=30,165)	*P* value
Sex			>.99
Female	59,852 (49.6)	14,963 (49.6)	
Male	60,808 (50.4)	15,202 (50.4)	
Age (y)			>.99
20-29	33,108 (27.4)	8277 (27.4)	
30-39	22,816 (18.9)	5704 (18.9)	
40-49	22,716 (18.8)	5679 (18.8)	
50-59	15,568 (12.9)	3892 (12.9)	
60-69	12,688 (10.5)	3172 (10.5)	
≥70	13,764 (11.4)	3441 (11.4)	
Mean ± SD	43.9±17.3	44.5±17.8	
Living in a low-urbanized area	31,478 (26.1)	9254 (30.7)	<.001
Low income[c]	2355 (1.9)	1253 (4.1)	<.001
Coexisting medical conditions			
Mental disorders	28,494 (23.6)	11,680 (38.7)	<.001
Hypertension	26,592 (22.0)	7398 (24.5)	<.001
COPD	18,102 (15.0)	6050 (20.1)	<.001
Hyperlipidemia	13,906 (11.5)	3826 (12.7)	<.001
Diabetes	10,826 (9.0)	3592 (11.9)	<.001
Migraine	7960 (6.6)	3553 (11.8)	<.001
Alcohol-related illnesses[d]	1317 (1.1)	1146 (3.8)	<.001
Parkinsonism	1635 (1.4)	934 (3.1)	<.001
Epilepsy	734 (0.6)	829 (2.8)	<.001
Smoking cessation	2273 (1.9)	806 (2.7)	<.001
Renal dialysis	799 (0.7)	353 (1.2)	<.001
New-onset stroke	2903 (2.4)	1455 (4.8)	<.001

[a]COPD = chronic obstructive pulmonary disease; TBI = traumatic brain injury.
[b]Data are given as No. (percentage) except where indicated otherwise.
[c]Low income was defined as patients qualifying for waived medical copayments as certified by the Bureau of National Health Insurance.
[d]Alcohol-related illnesses include alcoholic psychoses, alcohol dependence syndrome, alcohol abuse, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of the liver, and alcoholic liver damage.

receiving smoking cessation service (2.7% vs 1.9%), and renal dialysis (1.2% vs 0.7%) (*P*<.001 for all).

In the case-control study, the proportion of TBI was higher in nonsurvival stroke cases than in stroke survivors (7.5% vs 4.6%, *P*=.002) (Table 2). Nonsurvival stroke had a higher proportion in men (61.4% vs 57.3%, *P*=.05), and adults aged 80 years and older (34.1% vs 18.7%, *P*<.001), as well as patients with low-income status (7.7% vs 4.6%, *P*=.006), diabetes (28.4% vs 23.3%, *P*=.005), mental disorders (22.9% vs 18.9%, *P*=.02), COPD (19.7% vs 13.3%, *P*<.001), parkinsonism (7.2% vs 4.0%, *P*<.001), renal dialysis (5.9% vs 2.0%, *P*<.001), and epilepsy (4.5% vs 2.5%, *P*=.002).

Compared with the non-TBI cohort, patients with TBI were more likely to experience a stroke (HR, 1.98; 95% CI, 1.86-2.11) (Table 3). The HR for stroke associated with TBI was 1.96 (95% CI, 1.77-2.17) in women and 1.99 (95% CI, 1.82-2.16) in men. The association between TBI and risk of stroke was significant in all the age groups. In the case-control study, patients with TBI had a higher poststroke mortality rate compared with patients without TBI during the 24 months before stroke (OR, 1.57; 95% CI, 1.13-2.19). The OR for poststroke mortality associated with TBI was significant in men (OR, 1.92; 95% CI, 1.29-2.87). In the age-stratified analysis, the association between TBI and poststroke mortality was significant in patients with stroke aged 20 to 69 years.

Patients with mild TBI (HR, 1.74; 95% CI, 1.57-1.93), severe TBI (HR, 2.04; 95% CI, 1.89-2.20), and skull fracture (HR, 3.00; 95% CI, 2.42-3.71) were at increased risk for stroke (Table 4). Compared with the non-TBI cohort, patients with brain hemorrhage (HR, 2.69; 95% CI, 2.43-2.99) had a significant risk of stroke. In the case-control study, severe TBI (OR, 1.70; 95% CI, 1.13-2.55), brain hemorrhage (OR, 1.87; 95% CI, 1.15-3.04), and loss of consciousness (OR, 2.80; 95% CI, 1.27-6.17) were risk factors for subsequent poststroke mortality.

Table 5 gives the risk of stroke and poststroke mortality associated with the characteristics of TBI. Compared with the non-TBI cohort, the TBI cohort with 2 or more visits for emergency services (HR, 3.37; 95% CI, 2.88-3.95) or hospitalization for 7 or more days (HR, 3.14; 95% CI, 2.77-3.56) owing to TBI had a relatively high risk of stroke. Higher HRs for stroke were also found in patients with high medical expenditures for TBI care with a biological gradient relationship (HR, 2.26; 95% CI, 2.09-2.43). Low income (HR, 2.65; 95% CI, 2.16-3.25) is also associated with risk of stroke for the TBI cohort. In patients with stroke in the case-control study, factors associated with poststroke mortality included accessing emergency care for TBI (OR, 1.68; 95% CI, 1.09-2.59), hospitalization for 7 days or more for TBI (OR, 2.40; 95% CI, 1.13-5.12), high medical expenditures for TBI care during the 24 months before stroke (OR, 1.62; 95% CI, 1.08-2.44), low-income status

(OR, 3.22; 95% CI, 1.15-8.99), and migraine (OR, 3.05; 95% CI, 1.00-9.32).

DISCUSSION

The present 2 population-based studies found that patients with TBI during the 24 months before the study were at significantly higher risk for stroke in severity-dependent patterns. The risk of stroke and poststroke mortality were highly associated with the intensity of prestroke TBI-related health care and complications. To our knowledge, this is the first study to investigate the severity and characteristics of TBI related to stroke risk and the first study about the association of prestroke severity of TBI and poststroke mortality.

The results of this nationwide investigation were consistent with those of previous studies that found that male sex, older age, low-income status, and living in very urbanized areas were factors associated with poststroke mortality.[3-6,30] One possible explanation was that older people limited by movement disorders, reduced physical activity, more coexisting medical conditions, and polypharmacy might experience stroke.[1-5] Men had higher risks of TBI, stroke, and poststroke mortality than women owing to greater exposure to perilous jobs, dangerous activities, unhealthy lifestyles, and coexisting medical conditions.[31-33] In contrast, better outcomes in women after TBI or stroke might be due to female hormones and supplemental estrogen therapy.[31,34] Low-income people were more likely to be blue-collar workers living in hazardous environments, and they were likely to have had less knowledge about stroke prevention or recognition. These factors could all contribute to potential delays before medical care and could lead to worse outcomes after stroke. Higher poststroke mortality was seen in patients in highly urbanized areas, who are more at risk for traffic accidents, violence, and suicidal behaviors that can lead to TBI. Traumatic brain injury has been recognized as a risk factor for stroke.[35] Consistent with previous studies,[3-6] we found that hypertension, diabetes, mental disorders, COPD, hyperlipidemia, parkinsonism, migraine, renal dialysis, smoking, and alcohol drinking were factors associated with stroke or poststroke mortality. To validate whether TBI was a risk factor for stroke or poststroke mortality, we considered age, sex, urbanization, low-income status, and coexisting medical conditions as potential confounding factors that were adjusted in the regression analysis.

TABLE 2. Characteristics of Patients With Stroke With and Without Mortality[a]

Characteristic	Poststroke mortality (No. [%])[b] Survival (n=7153)	Mortality (n=598)	*P* value
Prestroke TBI[c]			.002
No	6821 (95.4)	553 (92.5)	
Yes	332 (4.6)	45 (7.5)	
Sex			.05
Female	3056 (42.7)	231 (38.6)	
Male	4097 (57.3)	367 (61.4)	
Age (y)			<.001
20-29	48 (0.7)	3 (0.5)	
30-39	154 (2.2)	11 (1.8)	
40-49	618 (8.6)	52 (8.7)	
50-59	1311 (18.3)	76 (12.7)	
60-69	1612 (22.5)	80 (13.4)	
70-79	2072 (29.0)	172 (28.8)	
≥80	1338 (18.7)	204 (34.1)	
Living in a very urbanized area	2106 (29.4)	108 (18.1)	<.001
Low-income status	327 (4.6)	46 (7.7)	.006
Coexisting medical conditions[c]			
Hypertension	3448 (48.2)	264 (44.2)	.06
Diabetes	1669 (23.3)	170 (28.4)	.005
Mental disorders	1352 (18.9)	137 (22.9)	.02
COPD	954 (13.3)	118 (19.7)	<.001
Parkinsonism	287 (4.0)	43 (7.2)	<.001
Renal dialysis	145 (2.0)	35 (5.9)	<.001
Epilepsy	175 (2.5)	27 (4.5)	.002
Hyperlipidemia	373 (5.2)	22 (3.7)	.10
Migraine	202 (2.8)	12 (2.0)	.24
Alcohol-related disease	68 (1.0)	7 (1.2)	.60
Smoking cessation	81 (1.1)	5 (0.8)	.51

[a]COPD = chronic obstructive pulmonary disease; TBI = traumatic brain injury.
[b]In-hospital death during admission for stroke.
[c]Within 24 months before a stroke event.

After adjustment, we found that TBI was associated with stroke and was significant in men, women, and all age groups. However, the association between TBI and poststroke mortality was significant only in men and in patients aged 20 to 69 years. A previous study reported that outcomes after TBI were worse in males than in females.[27] In the present study, mortality after stroke was higher in men than in women. These 2 findings may explain why we found that TBI predicted poststroke mortality well in men. Compared with people aged 20 to 69 years, older adults had more coexisting medical conditions that contributed to poststroke mortality. Thus, we found that TBI was a risk factor for poststroke mortality in people aged 20 to 69 years.

TABLE 3. Risk of Stroke and Poststroke Mortality Associated With Prestroke TBI Stratified by Age and Sex[a]

Feature	Stroke risk[b]		Poststroke mortality	
	Participants (No.)	HR (95% CI)	Participants (No.)	OR (95% CI)
Prestroke TBI[c]				
No	120,660	1 [Reference]	7374	1 [Reference]
Yes	30,165	1.98 (1.86-2.11)	377	1.57 (1.13-2.19)
Sex stratification[d]				
Female				
No TBI	59,852	1 [Reference]	3135	1 [Reference]
TBI	14,963	1.96 (1.77-2.17)	152	1.00 (0.53-1.88)
Male				
No TBI	60,808	1 [Reference]	4239	1 [Reference]
TBI	15,202	1.99 (1.82-2.16)	225	1.92 (1.29-2.87)
Age stratification[e]				
20-49 y				
No TBI	78,640	1 [Reference]	837	1 [Reference]
TBI	19,660	2.88 (2.45-3.39)	49	2.45 (1.02-5.86)
50-69 y				
No TBI	28,256	1 [Reference]	2945	1 [Reference]
TBI	7064	1.81 (1.63-2.01)	134	2.31 (1.27-4.18)
≥70 y				
No TBI	13,764	1 [Reference]	3592	1 [Reference]
TBI	3441	1.77 (1.61-1.95)	194	1.22 (0.78-1.92)

[a]HR, hazard ratio; OR = odds ratio; TBI = traumatic brain injury.

[b]When excluding stroke after TBI within 7 days: HR, 1.89 (95% CI, 1.75-1.99); when excluding stroke after TBI within 30 days: HR, 1.82 (95% CI, 1.69-1.93); TBI associated with ischemic stroke risk: HR, 1.64 (95% CI, 1.49-1.81); and TBI associated with hemorrhagic stroke risk: HR, 4.13 (95% CI, 3.57-4.78).

[c]Adjusted for age, sex, urbanization, low income, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, hyperlipidemia, parkinsonism, migraine, epilepsy, renal dialysis, smoking cessation, and alcohol-related illnesses.

[d]Adjusted for all covariates except sex.

[e]Adjusted for all covariates except age.

Although the association between TBI and stroke risk was previously reported,[24] the study was limited by inadequate control of potential confounding factors and provided no information about the types, severity, characteristics, and complications of TBI associated with stroke; whether TBI was associated with poststroke mortality was still unclear. The present nationwide population-based study found increased risk of stroke and poststroke mortality in patients with TBI after controlling for stroke-related risk factors, including hypertension, diabetes, mental disorders, COPD, parkinsonism, renal dialysis, hyperlipidemia, migraine, alcohol-related disease, and smoking cessation. This analysis found that the severity of TBI indicated by prestroke emergency care, inpatient care, or high medical expenditure for TBI significantly contributed to stroke and poststroke mortality. Higher stroke risk and mortality were also found in low-income patients with TBI. Compared with people without TBI during the 24 months before the study, patients with TBI with mental disorders or epilepsy were more likely to develop stroke, but this did not affect poststroke mortality, which was inconsistent with a previous study reporting lower mortality rates in patients with schizophrenia after stroke.[35] Patients with TBI with brain hemorrhage or loss of consciousness had increased stroke risk and poststroke mortality. In this study, receiving emergency care for TBI more than twice was the most significant factor for predicting stroke, and brain hemorrhage was the most important risk factor for poststroke mortality. To our knowledge, this is the first study reporting increased mortality after stroke in patients with TBI in a severity-dependent pattern.

Although the exact mechanisms of the relationship between TBI and risk of stroke are still unclear, some potential explanations are suggested. First, TBI may cause damage or disturbance to cerebrovascular circulation, cerebral oxygen metabolism, blood supply,

TABLE 4. Risk of Stroke and Poststroke Mortality Associated With Types of Prestroke TBI[a]

Feature	Stroke risk		Poststroke mortality	
	Participants (No.)	HR (95% CI)[b]	Participants (No.)	OR (95% CI)[b]
Type of prestroke TBI[c]				
No TBI	120,660	1 [Reference]	7374	1 [Reference]
Mild TBI	10,623	1.74 (1.57-1.93)	122	1.43 (0.79-2.59)
Skull fracture	1281	3.00 (2.42-3.71)	27	1.10 (0.26-4.78)
Severe TBI	18,261	2.04 (1.89-2.20)	228	1.70 (1.13-2.55)
Prestroke TBI combined with brain hemorrhage				
No TBI	120,660	1 [Reference]	7374	1 [Reference]
TBI without brain hemorrhage	25,157	1.79 (1.67-1.93)	225	1.38 (0.89-2.15)
TBI with brain hemorrhage	5008	2.69 (2.43-2.99)	152	1.87 (1.15-3.04)
Prestroke TBI combined with loss of consciousness				
No TBI	120,660	1 [Reference]	7374	1 [Reference]
TBI without loss of consciousness	27,206	1.99 (1.86-2.12)	331	1.43 (0.99-2.06)
TBI with loss of consciousness	2959	1.92 (1.63-2.27)	46	2.80 (1.27-6.17)

[a]HR, hazard ratio; OR = odds ratio; TBI = traumatic brain injury.
[b]Adjusted for age, sex, urbanization, low income, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, hyperlipidemia, parkinsonism, migraine, epilepsy, renal dialysis, smoking cessation, and alcohol-related illnesses.
[c]Within 24 months before a stroke event in the case-control study.

brain hemorrhage, and vascular deformity that significantly influence the occurrence of stroke.[36-39] The present study identified that brain hemorrhage significantly increased subsequent stroke and mortality. Second, people with physical disability caused by TBI may have limited physical activity, which was considered a risk factor for stroke. Third, mental disorders, epilepsy, and migraine were common complications in patients with TBI.[14-18] Antipsychotic medications and psychiatric diseases were also identified as risk factors for stroke.[8,40,41] Patients with posttraumatic psychiatric illness were more likely to have hypertension, diabetes, and hyperlipidemia, considered traditional risk factors for stroke.[3-8] A previous study found increased risk of stroke in patients with epilepsy.[7] The association between migraine and stroke risk was also documented in a previous study.[42] Thus, we considered that TBI-related psychiatric illness and migraine might contribute to stroke risk.

This study has several limitations. First, this study was limited by the data from insurance claims; this might underestimate TBI because some patients with mild TBI may not seek medical treatment. Similarly, coexisting medical conditions might be underestimated. The impact of TBI on the risk of stroke and poststroke mortality may be underestimated. Second, the exact etiologies of TBI were not available in the reimbursement data, so it was unclear whether TBI resulted from violence, vehicle-related collisions, falls, firearms, sports injuries, or accidental or nonaccidental causes. Third, this study has no data on patients' lifestyle and biomedical measures associated with stroke. Fourth, the inclusion of hemorrhagic stroke as the outcome is a study limitation because it may be sequelae of TBI. Although the clinical physicians could easily determine whether cerebral hemorrhage is internal intracerebral hemorrhage or traumatic brain hemorrhage, the low possibility of misdiagnosis is still a limitation. Fifth, although the effect of migraine was controlled in the multiple regressions when investigating whether TBI is associated with stroke or poststroke mortality, sometimes it may be difficult for physicians to differentiate between the presence of migraine with and without aura in the clinical setting. Furthermore, the definition of severity of TBI was entirely based on *ICD-9-CM* codes from the claims of the National Health Insurance Research Database.[29] The classification of severity of TBI should be more clearly defined. Finally, although we controlled for several confounders, residual confounding is always possible because there were still some vascular risk factors and other comorbidities that were not considered in this study.

TABLE 5. Risk of Stroke and Poststroke Mortality Associated With Severity of Prestroke TBI[a]

Characteristic	Stroke risk		Poststroke mortality	
	Participants (No.)	HR (95% CI)[b]	Participants (No.)	OR (95% CI)[b]
Prestroke emergency care for TBI[c]				
No TBI	120,660	1 [Reference]	7374	1 [Reference]
TBI without emergency care	14,474	1.89 (1.74-2.06)	133	1.61 (0.93-2.77)
TBI with 1 visit for emergency care	13,825	1.87 (1.71-2.05)	208	1.68 (1.09-2.59)
TBI with ≥2 visits for emergency care	1866	3.37 (2.88-3.95)	36	0.93 (0.28-3.13)
Prestroke inpatient care bed days for TBI[c]				
No TBI	120,660	1 [Reference]	7374	1 [Reference]
TBI without inpatient care	21,486	1.77 (1.64-1.91)	266	1.47 (0.98-2.20)
TBI with inpatient care <7 d	5997	2.02 (1.79-2.27)	63	1.38 (0.61-3.11)
TBI with inpatient care ≥7 d	2682	3.14 (2.77-3.56)	48	2.40 (1.13-5.12)
Medical expenditures for prestroke TBI care[c]				
No TBI	120,660	1 [Reference]	7374	1 [Reference]
Low	7542	1.66 (1.46-1.89)	57	1.06 (0.38-2.97)
Moderate	7543	1.60 (1.41-1.82)	80	1.74 (0.90-3.36)
High	15,080	2.26 (2.09-2.43)	240	1.62 (1.08-2.44)
Low-income status[c]				
No prestroke TBI	120,660	1 [Reference]	7374	1 [Reference]
Prestroke TBI without low income	28,912	1.96 (1.83-2.09)	354	1.48 (1.04-2.10)
Prestroke TBI with low income	1253	2.65 (2.16-3.25)	23	3.22 (1.15-8.99)
Effects of migraine[c]				
No prestroke TBI	120,660	1 [Reference]	7374	1 [Reference]
Prestroke TBI without migraine	28,116	2.00 (1.87-2.14)	356	1.49 (1.05-2.11)
Prestroke TBI with migraine	2049	1.56 (1.22-2.00)	21	3.05 (1.00-9.32)

[a]HR, hazard ratio; OR = odds ratio; TBI = traumatic brain injury.
[b]Adjusted for age, sex, urbanization, low income, hypertension, diabetes, mental disorders, chronic obstructive pulmonary disease, hyperlipidemia, parkinsonism, migraine, epilepsy, renal dialysis, smoking cessation, and alcohol-related illnesses.
[c]Within 24 months before a stroke event in the case-control study.

CONCLUSION

The nationwide retrospective cohort study and the case-control study successfully found that TBI was associated with risk of stroke and poststroke mortality. In particular, TBI survivors with severe TBI, brain hemorrhage, loss of consciousness, emergency care, inpatient care, low-income status, and migraine face increased risk of stroke and poststroke mortality. These data further showed that medical expenditure for TBI was associated with stroke risk and poststroke mortality in a dose-dependent relationship.

This study indicated many characteristics of TBI survivors who were at increased risk for stroke. Strategies to prevent stroke and meticulous care to reduce poststroke mortality should be routinely considered for this specific population with TBI. We suggest that rehabilitation programs for TBI survivors need to consider stroke prevention, including preventive medication (such as aspirin, warfarin, and statins), regular checkups (such as blood pressure, blood lipid levels, and fasting glucose concentrations), and cessation of smoking and alcohol drinking. In addition, physical therapy to increase TBI survivors' physical activity is also an important issue for TBI survivors to prevent stroke events. Further studies are needed to develop strategies to decrease stroke risks and outcomes for this challenging population.

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Abbreviations and Acronyms: **COPD** = chronic obstructive pulmonary disease; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; **OR** = odds ratio; **TBI** = traumatic brain injury

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REFERENCES

1. Feigin VL. Stroke in developing countries: can the epidemic be stopped and outcomes improved? *Lancet Neurol*. 2007;6(2):94-97.
2. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol*. 2007;6(2):182-187.
3. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-123.
4. Liao CC, Su TC, Sung FC, et al. Does hepatitis C virus infection increase the risk for stroke? a population-based cohort study. *PLoS One*. 2012;7(2):e31527.
5. Chou YC, Liao CC, Su LT, Yang PY, Sung FC. Stroke rehabilitation is associated with a reduction in dementia risk: a population-based retrospective cohort study. *J Rehabil Med*. 2012;44(4):319-324.
6. Wang IK, Chang SN, Liao CC, et al. Hypertensive disorders in pregnancy and preterm delivery and subsequent stroke in Asian women: a retrospective cohort study. *Stroke*. 2011;42(3):716-721.
7. Chang CC, Hu CJ, Lam F, Chang H, Liao CC, Chen TL. Postoperative adverse outcomes in surgical patients with epilepsy: a population-based study. *Epilepsia*. 2012;53(6):987-994.
8. Hu CJ, Liao CC, Chang CC, Wu CH, Chen TL. Postoperative adverse outcomes in surgical patients with dementia: a retrospective cohort study. *World J Surg*. 2012;36(9):2051-2058.
9. Faul M, Xu L, Wald MM, Coronado VG. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Death 2002-2006*. Atlanta, GA: Centers for Disease Control and Prevention; 2010.
10. DeKosky ST, Ikonomovic MD, Gandy S. Traumatic brain injury: football, warfare, and long-term effects. *N Engl J Med*. 2010;363(14):1293-1296.
11. Fleminger S, Ponsford J. Long-term outcome after traumatic brain injury. *BMJ*. 2005;331(7530):1419-1420.
12. Polusny MA, Kehle SM, Nelson NW, Erbes CR, Arbisi PA, Thuras P. Longitudinal effects of mild traumatic brain injury and posttraumatic stress disorder comorbidity on postdeployment outcomes in National Guard soldiers deployed to Iraq. *Arch Gen Psychiatry*. 2011;68(1):79-89.
13. Brown AW, Moessner AM, Mandrekar J, Diehl NN, Leibson CL, Malec JF. A survey of very-long-term outcomes after traumatic brain injury among members of a population-based incident cohort. *J Neurotrauma*. 2011;28(2):167-176.
14. Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. *Lancet*. 2009;373(9669):1105-1110.
15. Hesdorffer DC, Rauch SL, Tamminga CA. Long-term psychiatric outcomes following traumatic brain injury: a review of the literature. *J Head Trauma Rehabil*. 2009;24(6):452-459.
16. Bazarian JJ, Cernak I, Noble-Haeusslein L, Potolicchio S, Temkin N. Long-term neurologic outcomes after traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):439-451.
17. Dikmen SS, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):430-438.
18. Ishibe N, Wlordarczyk RC, Fulco C. Overview of the Institute of Medicine's committee search strategy and review process for Gulf War and health: long-term consequences of traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):424-429.
19. Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. *J Head Trauma Rehabil*. 2010;25(2):72-80.
20. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *Lancet*. 2012;380(9847):1088-1098.
21. Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology*. 1995;45(7):1253-1260.
22. Engberg AW. A Danish national strategy for treatment and rehabilitation after acquired brain injury. *J Head Trauma Rehabil*. 2007;22(4):221-228.
23. Patel HC, Bouamra O, Woodford M, et al. Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study. *Lancet*. 2005;366(9496):1538-1544.
24. Chen YH, Kang JH, Lin HC. Patients with traumatic brain injury: population-based study suggests increased risk of stroke. *Stroke*. 2011;42(10):2733-2739.
25. Burke JF, Stulc JL, Skolarus LE, Sears ED, Zahuranec DB, Morgenstern LB. Traumatic brain injury may be an independent risk factor for stroke. *Neurology*. 2013;81(1):33-39.
26. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf*. 2011;20(3):236-242.
27. Liao CC, Chiu WT, Yeh CC, Chang HC, Chen TL. Risk and outcomes for traumatic brain injury in patients with mental disorders. *J Neurol Neurosurg Psychiatry*. 2012;83(12):1186-1192.
28. Liao CC, Chang HC, Yeh CC, Chou YC, Chiu WT, Chen TL. Socioeconomic deprivation and associated risk factors of traumatic brain injury in children. *J Trauma Acute Care Surg*. 2012;73(5):1327-1331.
29. Yeh CC, Chen TL, Hu CJ, Chiu WT, Liao CC. Risk of epilepsy after traumatic brain injury: a retrospective population-based cohort study. *J Neurol Neurosurg Psychiatry*. 2013;84(4):441-445.
30. Nishi N, Sugiyama H, Kasagi F, et al. Urban-rural difference in stroke mortality from a 19-year cohort study of the Japanese general population: NIPPON DATA80. *Soc Sci Med*. 2007;65(4):822-832.
31. Cauley JA, Seeley DG, Ensrud K, et al. Estrogen replacement therapy and fractures in older women. *Ann Intern Med*. 1995;122(1):9-16.
32. Demetriades D, Kuncir E, Brown CV, et al. Early prediction of mortality in isolated head injury patients: a new predictive model. *J Trauma*. 2006;61(4):868-872.
33. Shih CC, Liao CC, Su YC, Tsai CC, Lin JG. Gender differences in traditional Chinese medicine use among adults in Taiwan. *PLoS One*. 2012;7(4):e32540.
34. Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal oestrogen treatment and stroke: a prospective study. *BMJ*. 1988;297(6647):519-522.
35. Kang JH, Xirasagar S, Lin HC. Lower mortality among stroke patients with schizophrenia: a nationwide population-based study. *Psychosom Med*. 2011;73(1):106-111.
36. Chan KH, Miller JD, Dearden NM. Intracranial blood flow velocity after head injury: relationship to severity of injury, time, neurological status and outcome. *J Neurol Neurosurg Psychiatry*. 1992;55(9):787-791.

37. Steiner LA, Coles JP, Czosnyka M, et al. Cerebrovascular pressure reactivity is related to global cerebral oxygen metabolism after head injury. *J Neurol Neurosurg Psychiatry*. 2003;74(6):765-770.
38. Marino S, Zei E, Battaglini M, et al. Acute metabolic brain changes following traumatic brain injury and their relevance to clinical severity and outcome. *J Neurol Neurosurg Psychiatry*. 2007;78(5):501-507.
39. Garnett MR, Blamire AM, Rajagopalan B, Styles P, Cadoux-Hudson TA. Evidence for cellular damage in normal-appearing white matter correlates with injury severity in patients following traumatic brain injury: a magnetic resonance spectroscopy study. *Brain*. 2000;123(pt 7):1403-1409.
40. Tsai KY, Lee CC, Chou YM, Su CY, Chou FH. The incidence and relative risk of stroke in patients with schizophrenia: a five-year follow-up study. *Schizophr Res*. 2012;138(1):41-47.
41. Lin HC, Hsiao FH, Pfeiffer S, Hwang YT, Lee HC. An increased risk of stroke among young schizophrenia patients. *Schizophr Res*. 2008;101(1-3):234-241.
42. Kurth T, Chabriat H, Bousser MG. Migraine and stroke: a complex association with clinical implications. *Lancet Neurol*. 2012;11(1):92-100.